Applications of DNA technology for cancer diagnosis and therapy

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SUMMARY

Chapter 1 is a review on genetic manipulations of T cell receptors (TCRs). Such manipulations have both the purpose to gain basic knowledge about TCRs characteristics and to exploit cytotoxic T lymphocyte (CTL) specificity of killing, an attractive tool for intervention. In this chapter the major strategies adopted to genetically manipulate TCRs are described: production of soluble single-chain TCRs, production of chimeric TCRs and production of T-bodies, the latter are the most frequently applied for therapeutical purposes.

Chapter 2 describes a strategy aimed at the ex-vivo retargeting of T cells by means of TCR gene transfer. In this chapter it is shown that a T cell line can be successfully transduced with a retroviral vector containing the full-length cDNA encoding for the α and the β chain of the TCR specific against the tumor antigen MAGE-3, presented in the context of the HLA class I allele A2.1. MAGE-3 is a very specific tumor antigen, expressed by many histological different tumor types. We conclude that this approach could represent a powerful therapeutical tool to genetically modify T lymphocytes of cancer patients.

Chapter 3 contains the evaluation of a ganciclovir analogue as tracer for repeated and non invasive PET imaging of the expression of the herpes simplex virus thymidine kinase (HSV-tk) gene. In this chapter it is demonstrated that the ganciclovir analogue ^{18}[F]FHPG is a promising tracer for monitoring HSV-tk enzyme activity in-vivo with PET, as clear images, with high target to non-target ratios were obtained.

Chapter 4 reviews another aspect of genetic manipulation, namely the use of antisense oligonucleotides (AS ODNs) or ribozymes to specifically inhibit the function of crucial genes, for instance oncogenes. These small molecules can be either externally provided or expressed within cells by means of gene transfer via adenoviral or retroviral vectors.

These strategies have led to a better understanding of several cellular and molecular mechanisms, among which cancer development. Moreover, both AS ODNs and ribozymes have been applied for therapeutical trials in diseases such as AIDS and cancer.

Chapter 5 contains a technical paper in which the difference in sensitivity of the nested reverse transcriptase polymerase chain reaction (RT-PCR) for tyrosinase is analyzed and quantified, with respect to the method utilized to produce the template c-DNA. In particular we found a difference of a factor 10 in favor of a specific priming versus a random one.

Chapter 6 deals with the reliability of the nested RT-PCR for tyrosinase for the early detection of micro metastasis in the lymph-nodes of malignant melanoma (MM) patients. The specificity of the assay was studied in lymph-nodes of 9 patients without MM. Based on the finding that 6 of 9 non-melanoma lymph nodes were positive in this assay we conclude that this assay can not be used for such a purpose. There are two possible explanations for this finding: first, tyrosinase expression comes from the few melanocytes or Schwann cells which may be present in the sample and are not detectable with less sensitive methods. Another explanation is the "illegitimate transcription" phenomenon, according to which the transcription regulation of some "luxury" genes is "leaky", thus enabling their expression also in cells in which the enzyme is not needed.

In **Chapter 7** some conclusions are given, concerning the use of DNA technology for cancer diagnosis and therapy. Furthermore, in this chapter possible future applications and strategies are suggested.